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Article

Epidemiological Characteristics and Risk Factors for Coronary Artery Lesions in Kawasaki Disease: A Five-Year Study in Xuzhou of 1082 Cases

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Abstract

Background: Kawasaki disease (KD) is a major cause of childhood vasculitis and a common cause of acquired heart disease in children worldwide. This study sought to investigate the epidemiological characteristics of KD and to analyze the risk factors associated with KD complications, particularly coronary artery lesions (CALs). **Methods**: The medical records of children diagnosed with KD in Xuzhou from January 1, 2016, to December 31, 2020, were reviewed retrospectively. Categorical variables were analyzed using the Chi-square test, while unpaired Student's *t*-tests or the Mann–Whitney U test were employed for continuous data. Univariate and multivariable logistic regression analyses were conducted to identify risk factors of KD- associated CALs. **Results**: Of the 1082 children enrolled, the male-to-female ratio was 1.7:1. The age at diagnosis ranged from 1 to 127 months, with a median of 17 months. Seasonal variation was observed, with a peak incidence noted in summer (27.5%). CALs were identified in 292 cases (27.0%), detailed as follows: transient dilation (17.4%), mild dilation (4.0%), small aneurysms (2.9%), medium-sized aneurysms (1.9%), and giant aneurysms (0.8%). Independent risk factors for CALs included male gender, longer fever duration before intravenous immunoglobulin (IVIG), and elevated levels of leukocytes, C-reactive protein, creatine kinase-muscle/brain (CK-MB), and interleukin-6 (IL-6). **Conclusions**: Male gender, elevated levels of fever duration before IVIG, leukocytes, C-reactive protein, CK-MB, and IL-6 were predictive risk factors of CALs. These findings underscore the need for increased clinical awareness and targeted interventions to mitigate the risk of CALs in children affected by KD.

Keywords

Kawasaki disease; epidemiology; coronary artery lesion

Introduction

Kawasaki disease (KD) is an acute, febrile disease of unknown etiology, predominantly affecting children under five years of age [1]. However, despite over fifty years of research since its initial description in 1967, the etiology of KD remains unknown [2,3]. A diagnosis of KD mainly relies on clinical manifestations and the exclusion of other clinically similar entities with known causes and without a specific diagnostic test [4]. Thus, analyzing the clinical characteristics of KD in children is crucial for its early recognition and timely initiation of appropriate treatment.

Coronary artery lesions (CALs), the main complication in KD, have emerged as the leading cause of acquired heart disease among children in developed countries [5]. A previous study reported KD in about 25% of untreated patients [6]. Although present clinical outcomes benefit largely from administering intravenous immunoglobulin (IVIG) together with aspirin, coronary intima damage might persist for a long time [7]. Thus, recent studies have focused on the risk factors of CALs, including demographic and clinical characteristics, laboratory variables, biomarkers, genetics, and others [8,9]. However, the results might differ due to different ethical backgrounds, social statuses, living environments, and economic conditions.

Xuzhou, a pivotal urban center in Northern Jiangsu Province, is home to a substantial population of approximately 9 million residents. Unfortunately, no such study has been carried out in our city regarding the clinical characteristics and risk factors of CALs. Therefore, this study aimed to identify significant risk factors for CALs and provide insights to guide clinical strategies and reduce the incidence of CALs.

Methods

Patients and Definitions

Medical records of children diagnosed with KD in The Affiliated Xuzhou Children's Hospital of Xuzhou Medical University from January 1, 2016, to December 31, 2020, were retrospectively reviewed. Diagnoses were confirmed by experienced pediatricians following the 2005 criteria of the Japanese Circulation Society [10]. These criteria included patients who had a fever for five or more days and at least four of the following symptoms: bilateral bulbar conjunctival injection, changes in the mucosa of the lips and oral cavity, polymorphous skin rash, peripheral extremity changes, and unilateral cervical lymphadenopathy. The diagnostic algorithm from the American Heart Association (AHA) guidelines [11] was employed to confirm the cases presenting fewer than four of the principal symptoms. Patients were excluded if they (1) initiated IVIG in other hospitals, (2) did not have IVIG treatment, (3) had incomplete medical data, and (4) had a second or third episode of KD.

Echocardiograms were routinely performed in all patients at three specific intervals: at the time of diagnosis, between 1 and 2 weeks, and 1 month post-diagnosis. This study specifically evaluated CALs, characterized by anomalies such as coronary artery dilation, coronary artery aneurysm, coronary artery stenosis, and occlusion, utilizing both coronary artery internal diameter measurements and Z-Score criteria [6]. Diagnostic categories were (1) normal coronary arteries, defined as a coronary artery diameter of $\leq$2.5 mm for patients aged between 0 and 3 years, $\leq$3.0 mm for those aged between 3 and 9 years, and $\leq$3.5 mm for patients over 9 years, all with a Z-Score of $<$2.0. (2) Transient dilation, characterized by a coronary artery internal diameter of $<$4.0 mm and a Z-Score between 2 and 2.5, identified within 1 month from disease onset. (3) Mild dilation, characterized by a coronary artery internal diameter of $<$4.0 mm and a Z-Score between 2 and 2.5, observed after 1 month from the onset. (4) Small coronary artery aneurysm defined as a coronary artery internal diameter $<$4.0 mm, with a Z-Score between 2.5 and 5. (5) Medium-sized coronary artery aneurysm, defined as a coronary artery internal diameter between 4.0 and 8.0 mm and a Z-Score from 5 to 10. (6) Giant coronary artery aneurysm, defined as a coronary artery internal diameter $\geq$8.0 mm or a Z-Score $\geq$10 [12].

Clinical information was retrospectively collected from the Affiliated Xuzhou Children's Hospital of Xuzhou Medical University electronic medical record system, including gender, age, symptom duration, clinical manifestations, the duration of illness upon initiation of IVIG therapy, and the presence of concomitant CALs. Additionally, the study documented extensive laboratory variables, such as peripheral blood white blood cell (WBC) count, hemoglobin (HGB), C-reactive protein (CRP), platelet count (PLT), erythrocyte sedimentation rate (ESR), serum sodium (Na), plasma alanine aminotransferase (ALT), aspartate aminotransferase (AST), plasma serum protein (ALB), creatine kinase-muscle/brain (CK-MB), interleukin-6 (IL-6), procalcitonin (PCT), and total bilirubin (TBiL). The Ethics Committee of The Affiliated Xuzhou Children's Hospital of Xuzhou Medical University approved this study (approval number: 2022-S-01-K01).

Statistical Analysis

Data were entered twice into EpiData version 3.1 (EpiData Association, Odense, Denmark) to ensure consistency. Statistical analyses were performed using SPSS version 25.0 for Windows (SPSS Inc, Chicago, IL, USA). Continuous variables are expressed as the mean $\pm$ standard deviation (SD) or median (quartiles), while categorical variables are presented as numbers with percentages. Parametric and nonparametric comparative tests for continuous data and χ^2 tests for categorical data were used to compare variables between the two groups. Variables expressing a value of $p < 0.05$ in the univariate analysis were included in the multivariable analysis. We additionally carried out a stratification analysis to confirm our results. We grouped all patients into two groups based on the median age, $<$17 months and $\geq$17 months, and performed the multivariable regression again. A two-sided value of $p < 0.05$ was considered statistically significant.

Results

General Demographics

A total of 1082 patients were enrolled in this study, with 684 (63.2%) males and 398 (36.8%) females, meaning the male-to-female ratio was 1.7:1. The median age of the patients at diagnosis was 17.0 months. Diagnoses peaked at 1 year of age. Distribution by age included 35 (3.2%) cases occurring before 3 months, 174 (16.1%) cases before 6 months, 377 (34.8%) cases before 1 year, and 687 (63.5%) cases before 2 years. Only 74 (6.8%) patients were older than 5 years (Fig. 1).

Monthly and Seasonal Distribution of KD

The monthly distribution of KD showed a seasonal variation, peaking in the summer months of June to August, accounting for 298 (27.5%) cases. Fewer cases were recorded in the autumn (September to November) and winter (December to February) seasons, with 250 (23.1%) cases and 259 (23.9%) cases, respectively. Significant spikes were observed in May and July, with 308 (28.5%) cumulative cases reported. KD occurred least frequently in September (6.8%) (Fig. 2).

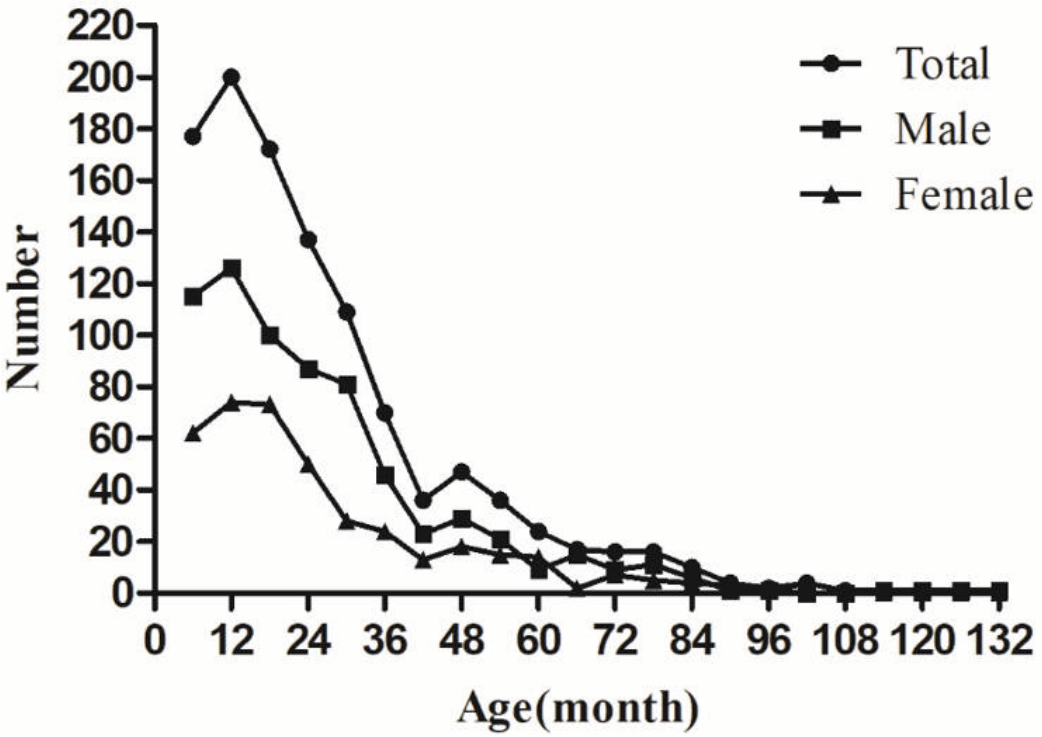

Fig. 1. Age distribution of onset of Kawasaki disease.

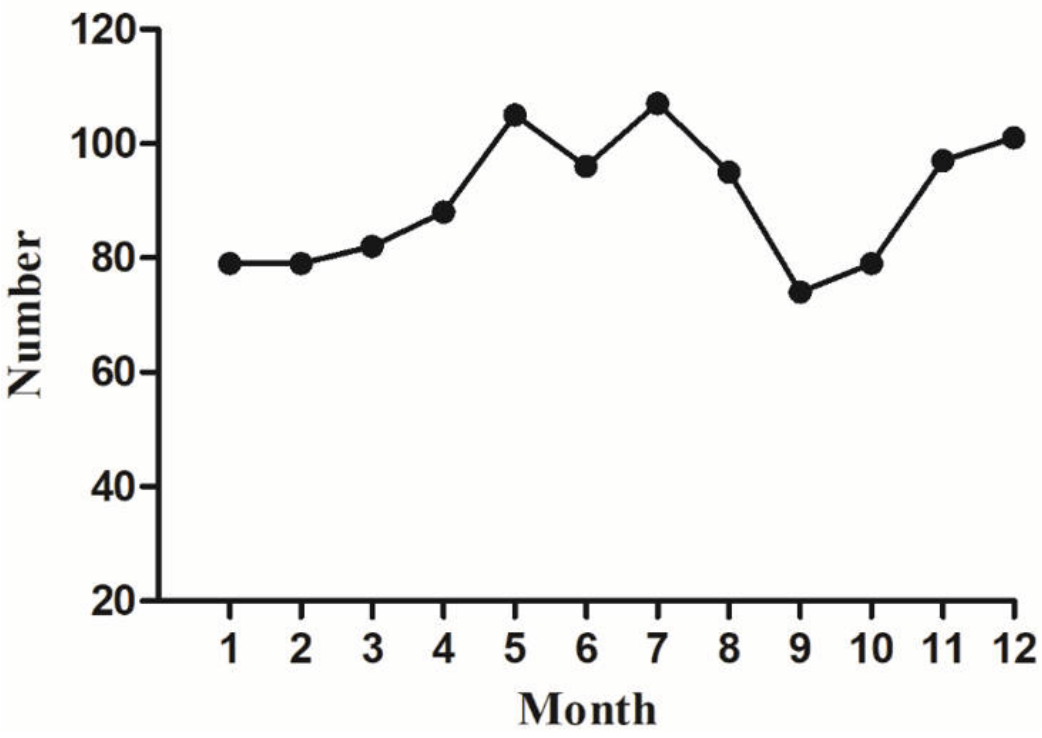

Fig. 2. Monthly distribution of Kawasaki disease.

Clinical Manifestations

Fever was the predominant clinical feature in KD and persisted for a median of 7 (6–8) days. Changes in the lips and oral cavity were observed in 987 (91.2%) cases. This was closely followed by bilateral conjunctival congestion in 975 (90.1%) cases. Other symptoms included cervical lymphadenopathy (848 cases, 78.4%), polymorphous exanthema (821 cases, 75.9%), and changes in peripheral extremities (727 cases, 67.2%). Perianal peeling and ery-

Table 1. Univariate analysis of relevant factors for coronary artery lesions.

Variables	CALs	No CALs	*p*
Number, n (%)	292 (27.0)	790 (73.0)	-
Male, n (%)	213 (72.9)	417 (59.6)	<0.001
Age, months, median (quartiles)	16 (7, 29)	17.5 (8, 31)	0.356
Fever duration before IVIG, days, mean ± SD	8.3 ± 3.5	6.9 ± 2.1	<0.001
ESR, mm/h, mean ± SD	58.3 ± 19.7	48.6 ± 19.6	0.826
HGB, g/L, mean ± SD	108.6 ± 13.1	109.4 ± 16.4	0.468
ALB, g/L, mean ± SD	38.55 ± 8.38	39.20 ± 7.00	0.228
Na, mmol/L, mean ± SD	137.24 ± 3.27	137.03 ± 5.74	0.582
WBC, 10^9/L, median (quartiles)	16.1 (13.1, 20.6)	14.8 (11.4, 18.6)	<0.001
CRP, mg/L, median (quartiles)	69.0 (41.4, 110.0)	61.7 (38.4, 94.3)	0.018
PLT, 10^9/L, median (quartiles)	411.0 (313.5, 520.0)	366.5 (292.0, 466.5)	<0.001
ALT, U/L, median (quartiles)	32.0 (18.0, 64.0)	30.0 (16.0,83.5)	0.639
AST, U/L, median (quartiles)	32.0 (23.0, 46.0)	32.0 (24.0, 51.0)	0.095
TBiL, µmol/L, median (quartiles)	6.0 (4.1, 9.1)	6.9 (5.0, 10.1)	<0.001
CK-MB, U/L, median (quartiles)	20.0 (12.0, 35.0)	17.0 (12.0, 25.0)	0.002
PCT, ng/mL, median (quartiles)	0.5 (0.10, 1.30)	0.3 (0.09, 0.90)	0.012
IL-6, pg/mL, median (quartiles)	37.9 (16.4, 93.9)	29.5 (11.0, 80.1)	0.009

ALB, serum albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CALs, coronary artery lesions; CK-MB, creatine kinase-muscle/brain; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HGB, hemoglobin; IL-6, interleukin 6; IVIG, intravenous immunoglobulin; Na, serum sodium; PCT, procalcitonin; PLT, blood platelet count; SD, standard deviation; TBiL, total bilirubin; WBC, white blood cells.

thema, along with BCG inoculation site change, were less common, recorded in 305 (28.1%) and 242 (22.4%) cases, respectively.

Coronary Complications in KD

CALs were identified in 292 (27.0%) patients, including transient dilation (188 cases, 17.4%), mild dilation (43 cases, 4.0%), small coronary artery aneurysms (31 cases, 2.9%), medium-sized coronary artery aneurysms (21 cases, 1.9%), and giant coronary artery aneurysms (9 cases, 0.8%). No myocardial infarction or fatalities occurred during the study period.

Univariate Analysis of KD Complicated with CALs

Table 1 summarizes the laboratory and clinical data between patients with and without complications from CALs. The group with CALs exhibited significantly elevated WBC, PLT, CRP, CK-MB, PCT, and IL-6 levels. Conversely, TBiL levels were significantly reduced in the CALs group. Patients with CALs tended to be male and had a longer fever duration before IVIG initiation ($p < 0.05$). However, the two groups had no significant differences in age, ESR, HGB, ALB, Na, ALT, and AST ($p > 0.05$).

Binomial Logistic Regression Analysis for CALs

Multivariable logistic regression was then conducted using the significant variables selected in the univariate analysis. The results identified several independent risk factors: male gender, longer fever duration before IVIG, and higher levels of WBC, CRP, CK-MB, and IL-6 (Table 2). Among them, male gender was the most potent risk factor of CALs with an odds ratio of 1.861 (95% confidence interval (CI): 1.361–2.545).

Stratification Analysis for CALs

A stratification analysis regarding age was conducted to confirm the results; data are shown in Table 3. In patients younger than 17 months, males, a longer fever duration before IVIG and higher CRP, PLT, TBiL, CKMB, PCT, and IL-6 levels were identified as risk factors for CALs, while in patients older than 17 months, fever duration before IVIG, and higher CRP, CKMB, and IL-6 levels were considered as risk factors ($p < 0.05$).

Discussion

In the present study, we conducted a retrospective analysis of KD covering five years in a tertiary hospital in North Jiangsu Province. To our knowledge, this is the largest study of KD in this area. We found that the male-to-female ratio for children with KD was 1.7:1. The rate was highest in patients at one year of age, while more than 90% of KD patients were under 5 years. The occurrence of KD was higher in summer. The overall incidence of CALs was 27.0% when transient dilation was the most common. This

Table 2. Multivariate logistic regression analysis of risk factors for coronary artery lesions.

Variables	Odds ratio	95% confidence interval	*p*
Male gender	1.861	1.361–2.545	<0.001
Fever duration before IVIG	1.221	1.152–1.296	<0.001
WBC count	1.032	1.007–1.059	0.013
CRP	1.006	1.002–1.009	<0.001
PLT	1.001	1.000–1.002	0.062
TBil	0.987	0.968–1.006	0.170
CK-MB	1.019	1.010–1.027	<0.001
PCT	1.016	0.985–1.049	0.314
IL-6	1.001	1.000–1.002	0.008

CRP, C-reactive protein; CK-MB, creatine kinase-muscle/brain; IL-6, interleukin 6; IVIG, intravenous immunoglobulin; PCT, procalcitonin; PLT, blood platelet count; TBiL, total bilirubin; WBC, white blood cell.

Table 3. Stratification analysis of risk factors for coronary artery lesions.

Variables	Patients <17 months			Patients ≥17 months		
	Odds ratio	95% Confidence interval	*p*	Odds ratio	95% Confidence interval	*p*
Male gender	2.296	1.460–3.683	<0.001	1.540	1.001–2.404	0.053
Fever duration before IVIG	1.213	1.120–1.319	<0.001	1.233	1.132–1.350	<0.001
WBC count	1.028	0.991–1.067	0.135	1.035	0.999–1.073	0.056
CRP	1.005	1.001–1.010	0.027	1.006	1.001–1.010	0.010
PLT	1.001	1.000–1.003	0.045	1.001	0.999–1.002	0.440
TBil	0.941	0.896–0.982	0.008	0.998	0.977–1.018	0.875
CK-MB	1.014	1.001–1.026	0.028	1.022	1.010–1.034	<0.001
PCT	1.155	1.059–1.268	0.001	0.990	0.937–1.030	0.691
IL-6	1.001	0.999–1.003	0.221	1.001	1.000–1.002	0.038

CRP, C-reactive protein; CK-MB, creatine kinase-muscle/brain; IL-6, interleukin 6; IVIG, intravenous immunoglobulin; PCT, procalcitonin; PLT, blood platelet count; TBiL, total bilirubin; WBC, white blood cell.

study identified males with a longer fever duration before IVIG and higher levels of WBC, CRP, CK-MB, and IL-6 as potential risk factors for CALs.

Although a recent publication at a major medical institution in Shanghai, China, reported an upward trend in KD cases [13], we did not describe the occurrence of cases in our study due to the influence of the COVID-19 pandemic, which greatly impacted the disease occurrence. However, our study revealed novel insights into the seasonal trends of KD. Contrary to the study from Japan, which indicated a peak in KD cases in spring [14], our data identified summer as the season with the most cases, with fewer cases observed in winter. The divergence in seasonal distribution could partly elucidate the potential effect of environmental changes or infectious causes on the disease onset [15–17]. Summer is typically associated with a higher incidence of viral infections. A previous study has highlighted that atmospheric wind patterns, particularly in regions around the Pacific, might transport a microbial or toxic antigen responsible for triggering KD in genetically susceptible children [18]. Notably, the incidence of KD in Northeast Asian regions was markedly higher than in the US and European countries [19]. Overall, our results supported the hypothesis that infectious agents might trigger specific immune responses in individuals with genetic predispositions [20].

The gender disparity for KD also indicated other influential factors beyond infectious agents. The male-to-female ratio of 1.7:1 found in our study was consistent with the findings from Taiwan [21], Australia, the United Kingdom, and Sweden [22]; however, it was slightly higher than that reported in Japan [22] and Korea [23]. This difference in susceptibility between genders might be attributed to innate characteristics of KD, such as varying IL-1β expression and gender-specific genetic predispositions [24,25]. Moreover, studies in Japan assumed that a spectrum of etiological factors, including sex hormones and diverse genetic and environmental constituents, could partly underlie these gender-based variations [26].

In our study, the incidence of CALs was 27.0%, which was higher than that in several previous studies [13,27,28]. This discrepancy might arise from our definition of CALs, which incorporated both coronary artery internal diameter and Z-score evaluations. The traditional criteria, based solely on coronary artery dimensions, might underestimate the incidence [29]. Notably, the cause of CALs remains unclear; however, the risk factors identified in our study

partly align with those in previous publications, including elevated leukocyte counts [30,31] and male gender [32,33]. Moreover, KD patients with CALs often exhibited elevated myocardial enzymes and leukocyte counts, which indicated possible myocardial damage, cardiac dysfunction, and more severe systemic inflammatory responses, underscoring the importance of early cardiac enzyme and blood routine tests in children with KD.

Our data also highlighted elevated IL-6 and CRP levels as independent risk factors for CALs in KD. IL-6, which is secreted by various cells, is considered a proinflammatory cytokine and plays a crucial role in inflammatory and stress responses. As an initial cytokine in the inflammatory cascade, IL-6 acts as a primary mediator to induce CRP production. Our findings were in accordance with previous studies, which identified elevated IL-6 as a significant risk factor for concurrent KD and CALs [34,35]. These findings suggest intensive anti-inflammatory treatments should be initiated in patients with higher IL-6 and CRP levels to prevent CALs [36,37].

Prolonged fever duration before IVIG administration was another significant risk factor for developing CALs in our study. However, previous studies had determined that early administration of IVIG was not beneficial for coronary outcomes and was associated with a higher incidence of IVIG resistance [38,39]. A later study argued that early IVIG treatment were most likely due to the underlying higher initial disease severity [40,41]. Another study insisted that early IVIG treatment could effectively suppress systemic inflammation and minimize endothelial damage [42]. Thus, IVIG must be administered promptly once the diagnosis of KD is confirmed.

It should be noted that the risk factors identified in the stratification analysis were slightly different from those in the main results. Subsequently, we speculated that these differences were caused by the inclusion of fewer cases in each subgroup, which resulted in the *p*-value becoming somewhat non-significant. Fortunately, the odds ratios of the variables were in parallel with the main results. We found that higher levels of PLT and PCT and a lower level of TBiL were also indicative of CALs in younger patients, which could help physicians recognize potential CALs in these patients.

In conclusion, the development of CALs in KD is multifactorial. Timely identification of relevant risk factors and prompt intervention are critical in preventing the development of CALs. Early recognition of factors such as prolonged fever and elevated inflammatory markers indicates immediate IVIG administration and (or) adjunctive use of glucocorticoids and immunosuppressants to minimize the risk of CALs.

Our study had certain limitations. First, it was retrospective, which could produce selection biases. Second, it was a single-center study, which restricts the generalizability of our findings. Thus, a further multicenter and prospective study is warranted in the future. Additionally, the variability introduced by different echocardiographic physicians could influence the outcomes. Despite these limitations, the sample size was large enough to ensure an accurate presentation of the characteristics of KD and the risk factors associated with CALs.

Conclusions

Male gender, elevated levels of fever duration before IVIG, leukocytes, C-reactive protein, CK-MB, and IL-6 were predictive of CALs.

Availability of Data and Materials

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Author Contributions

LN, FW, YT, and HL: contributed to the study design and analysis, conducted the study, and performed the examinations. HX, YiX, YoX and XA: contributed to the collection and assembly of data. LN and HL: performed the statistical analysis, wrote the manuscript, and provided final approval of the manuscript. All authors contributed to editorial changes in the manuscript. All authors have read and approved the final version of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was carried out in accordance with the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of The Affiliated Xuzhou Children's Hospital of Xuzhou Medical University (No: 2022-S-01-K01). Informed consent was waived by the ethics Committee.

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Conflict of Interest

The authors declare no conflict of interest.

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